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New and Convenient Synthesis of 2-Substituted 2,3-Dihydro-1*H*-benz[de]isoquinolin-1-ones

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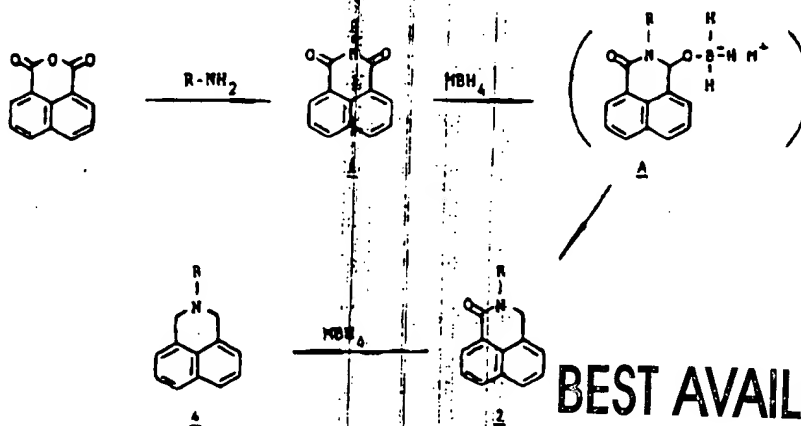
Synopsis. Various 2-substituted 2,3-dihydro-1*H*-benz[de]isoquinolin-1-ones were obtained in high yields by chemoselective reduction of 2-substituted 1*H*-benz[de]isoquinoline-1,3(2*H*)-diones with sodium or zinc borohydride at room temperature.

Although there have been many reports on the synthesis of isoindoles such as 2,3-dihydro-1*H*-isoindol-1-one,¹⁾ the synthesis of 2,3-dihydro-1*H*-benz[de]isoquinolin-1-ones (2) have little been studied. Thus, only two papers have been reported on the troublesome synthesis of isoquinoline 2 by electrolytic²⁾ and catalytic³⁾ reduction of 2-substituted 1*H*-benz[de]isoquinoline-1,3(2*H*)-diones (1). In the course of our investigations on the chemistry of isoindoles,⁴⁾ we have been looking for new and convenient method for synthesis of isoquinolines 2, which were novel heterocycles and considered to be versatile for synthesis of biologically active isoquinoline derivatives in connection with alkaloids.⁵⁾ It is well-known that carbonyl group of acid anhydride can be reduced to methylene group by sodium borohydride⁶⁾ but that of dicarboximides can not be reduced.⁷⁾ We could not find actually any example of such reduction in literatures. Therefore, our attempts to synthesize 2 were initially directed to the reactions of 1,8-naphthalenedicarbaldehydes with amines based on the previous results.⁷⁾ We could not, however, obtain 2-substituted isoquinolines 2 except for parent isoquinoline 2a. Meanwhile, a successful example of the demethoxylation of 2,3-dihydro-3-methoxy-1*H*-benz[de]isoquinolin-1-one to 2a with sodium borohydride by Warshawsky⁸⁾ was reported to stimulate us to examine selective reduction of 2-substituted 1*H*-benz[de]isoquinoline-1,3(2*H*)-diones (1), which were readily prepared by treating 1*H*,3*H*-

naphtho[1,8-*cd*]pyran-1,3-dione with various amines,⁹⁾ to 2 using sodium or zinc borohydride.¹⁰⁾ In this paper, we wish to report a new and convenient chemoselective synthesis of 2 (Scheme 1).

As shown in Table I, nine isoquinolines 2a-f and 2o-q having alkyl substituents were readily formed via intermediate A (Scheme 1) in high yields on treatment with sodium borohydride. When desired 2 could not be obtained from 1 with sodium borohydride, zinc borohydride was employed as a reductant to give 2 in moderate yields (Runs 7-11, 13, and 16) together with by-products, 2,3-dihydro-2-alkyl-1*H*-benz[de]isoquinoline (4b-k). It is noteworthy that the present reduction was compatible with hydroxyl, chloro, and carboxyl groups (Runs 13, 16, and 20-22). Interestingly, three new heterocycles 3l-n were obtained by treating 1l-n with sodium borohydride in moderate yields together with desired 2l-n, as shown in Table I. Moreover, an addition of magnesium perchlorate to the reaction system using sodium borohydride increased exceedingly the yields of cyclized products 3l-n (Runs 14, 17, and 19). Although the role of magnesium ion is not necessarily obvious, 3l-n seem to be formed by intramolecular migration of alkoxy group of intermediate B, in which boron coordinated¹¹⁾ with two oxygen atom of two hydroxyl groups in basic conditions as shown in Scheme 2.

8n was obtained as a mixture of two diastereomers. The results of Table I show that a bulky substituent in prevented the cyclization and 1o having five methylene chains did not give the corresponding cyclic compounds (Runs 18 and 20). In the reactions of 1l and 1m, the use of zinc borohydride afforded desired 2l and 2m preferentially (Runs 13 and 16). Although various solvents such as methanol or tetrahydrofuran were



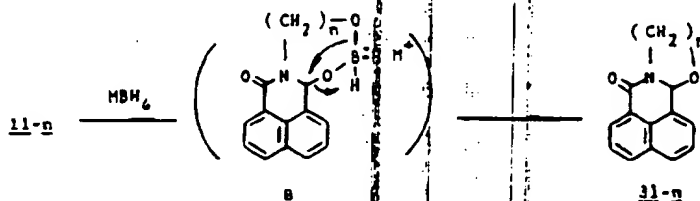
Scheme 1

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Table 1. The Chemoselective Reduction of Benzisoquinoline-1,3-diones 1

Run ^{a)}	Substrate R	1	React. time/h	Boro- hydride	Yield of product/% ^{b)}		
					2	3	4
1	H-	1a	24	NaBH ₄	97 2a ^{b)}	—	—
2	CH ₃ -	1b	24	NaBH ₄	94 2b	—	—
3	CH ₃ CH ₂ CH ₂ -	1c	24	NaBH ₄	98 2c	—	—
4	(CH ₃) ₂ CH-	1d	8	NaBH ₄	79 2d	—	—
5	CH ₃ -CH=CH-	1e	14	NaBH ₄	79 2e	—	—
6	CH ₃ CH ₂ CH ₂ CH ₂ -	1f	5	NaBH ₄	82 2f	—	—
7	C ₆ H ₁₁ -	1g	24	Zn(BH ₄) ₂	53 2g	—	—
8	C ₆ H ₅ -	1h	25	Zn(BH ₄) ₂	49 2h	—	13 4b ⁽¹²⁾
9	C ₆ H ₅ -CH ₂ -	1i	25	Zn(BH ₄) ₂	50 2i	—	20 4i ⁽¹²⁾
10	4-CH ₃ -C ₆ H ₄ -	1j	29	Zn(BH ₄) ₂	41 2j	—	24 4j ⁽¹²⁾
11	4-Cl-C ₆ H ₄ -	1k	23	Zn(BH ₄) ₂	49 2k	—	43 4k ⁽¹²⁾
12	HO-(CH ₂) ₂ -	1l	4	NaBH ₄	55 2l	22 3l	—
13	HO-(CH ₂) ₃ -	1l	27	Zn(BH ₄) ₂	32 2l	—	—
14 ^{c)}	HO-(CH ₂) ₄ -	1l	10	NaBH ₄	—	81 3l	—
15	HO-(CH ₂) ₂ -	1m	4	NaBH ₄	34 2m	55 3m	—
16	HO-(CH ₂) ₃ -	1m	28	Zn(BH ₄) ₂	36 2m	—	—
17 ^{c)}	HO-(CH ₂) ₄ -	1m	10	NaBH ₄	—	78 3m	—
18	HO-CH(CH ₃)CH ₂ -	1n	4	NaBH ₄	81 2n	9 3n ^{d)}	—
19 ^{c)}	HO-CH(CH ₃)CH ₂ -	1n	12	NaBH ₄	36 2n	55 3n ^{d)}	—
20	HO-(CH ₂) ₂ -	1o	4	NaBH ₄	68 2o	—	—
21	Cl-CH ₂ CH ₂ -	1p	4	NaBH ₄	73 2p	—	—
22	HOCO-(CH ₂) ₂ -	1q	4	NaBH ₄	83 2q	—	—

a) Reaction conditions: 1, 0.5 mmol; NaBH₄, 50 mmol; Zn(BH₄)₂, 10 mmol, r.t. b) Isolated yields based on the substrate. c) Mg(ClO₄)₂ (5 mmol) was added to the reaction system. d) A mixture of two diastereomer was obtained.



Scheme 2

nined in all cases, only ethanol-water gave prefer-
results.

Experimental

measurements. All the melting points were uncorrected. Spectra were obtained on a Hitachi 295 spectrophotometer and ¹H NMR spectra were obtained on a Hitachi R-22 spectrometer using tetramethylsilane as an internal standard. Mass spectra were taken with a Hitachi RMU-6M mass spectrometer. Elemental analyses were performed with a Jigimoto MT-3. All the reactions were carried out under nitrogen atmosphere and monitored by TLC (Merck elgel 60-GF).

Materials. All the reagents were obtained from Wako Chemical Industries Ltd., Tokyo Kasei Co. Ltd., or Nichi Chemical Co. The reagents used were further purified by usual methods such as recrystallization or distillation. Wako gel C-200 was used as a silica gel for column chromatography.

General Procedure. To a solution of sodium borohydride (5 mmol) in EtOH/H₂O (20 ml, v/v: 10/1) was added 1 mmol and then the mixture was stirred for 4 h at 25 °C. Quenching with aq. HCl, the reaction mixture was acidified with CH₂Cl₂ (20 ml). The combined organic phase was dried over MgSO₄ and evaporation of the solvent

followed by chromatography on silica gel gave colorless crystals, 2-substituted 2,3-dihydro-1H-benz[de]isoquinolin-1-one (2). Elemental analyses for 2d, 2e, and 2f were not available because of the lability and the difficulty of further purifications of these compounds.

2a, 2b, 4b⁽¹²⁾, 4c⁽¹²⁾, 4j⁽¹²⁾ and 4k⁽¹²⁾ was identified by comparison of the spectral and physical data with those of authentic sample.

2b: Mp 76 °C (from hexane-AcOEt); IR (KBr) 1610 and 1640 cm⁻¹; ¹H NMR (CDCl₃) δ=3.23 (s, 3H, CH₃), 4.93 (s, 2H, CH₂), and 7.20–8.36 (m, 6H, arom); MS (20 eV) m/z 195 (M⁺). Found: C, 79.17; H, 5.67; N, 7.02%. Calcd for C₁₅H₁₁NO: C, 79.17; H, 5.62; N, 7.10%.

2c: Mp 84 °C (from AcOEt); IR (KBr) 1620 and 1645 cm⁻¹; ¹H NMR (CDCl₃) δ=1.00 (t, 3H, J=7 Hz, CH₃), 1.76 (sex, 2H, J=7 Hz, CH₂), 3.64 (t, 2H, J=7 Hz, CH₂), 4.94 (s, 2H, CH₂), and 7.15–8.42 (m, 6H, arom); MS (20 eV) m/z 225 (M⁺). Found: C, 79.64; H, 6.78; N, 6.21%. Calcd for C₁₅H₁₃NO: C, 79.97; H, 6.71; N, 6.22%.

2d: Oil; IR (neat) 1620 and 1640 cm⁻¹; ¹H NMR (CDCl₃) δ=1.34 (d, 6H, J=8 Hz, CH₃), 4.86 (s, 2H, CH₂), 5.24 (sept, 1H, J=8 Hz, CH), and 7.27–8.44 (m, 6H, arom); MS (20 eV) m/z 225 (M⁺).

2e: Oil; IR (neat) 1610 and 1635 cm⁻¹; ¹H NMR (CDCl₃) δ=4.23–4.38 (m, 2H, CH₂), 4.88 (s, 2H, CH₂), 5.15–5.43 (m, 2H, CH₂), 5.68–6.23 (m, 1H, -CH=), and 7.17–8.40 (m,

6H, arom); MS (20 eV) m/z 223 (M^+).

2f: Oil; IR (neat) 1610 and 1635 cm^{-1} ; ^1H NMR (CDCl_3) δ =1.00 (t, 3H, J =7 Hz, CH_3), 1.24–1.93 (m, 4H, CH_2), 3.71 (t, 2H, J =7 Hz, CH_2), 4.97 (s, 2H, CH_2), and 7.27–8.46 (m, 6H, arom); MS (20 eV) m/z 239 (M^+).

2g: Mp 127°C (from AcOEt); IR (KBr) 1610 and 1630 cm^{-1} ; ^1H NMR (CDCl_3) δ =0.90–2.30 (m, 1H, cyclohexyl), 4.80 (s, 2H, CH_2), and 7.10–8.27 (m, 6H, arom); MS (70 eV) m/z 265 (M^+). Found: C, 81.67; H, 7.27; N, 5.35%. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}$: C, 81.48; H, 7.22; N, 5.28%.

2h: Mp 164°C (from AcOEt); IR (KBr) 1615 and 1640 cm^{-1} ; ^1H NMR (CDCl_3) δ =5.33 (s, 2H, CH_2) and 7.24–8.54 (m, 11H, arom); MS (70 eV) m/z 259 (M^+). Found: C, 83.36; H, 4.96; N, 5.31%. Calcd for $\text{C}_{18}\text{H}_{13}\text{NO}$: C, 83.38; H, 5.05; N, 5.40%.

2i: Mp 102°C (from AcOEt); IR (KBr) 1615 and 1640 cm^{-1} ; ^1H NMR (CDCl_3) δ =4.87 (s, 2H, CH_2), 4.93 (s, 2H, CH_2), and 7.15–8.55 (m, 11H, arom); MS (70 eV) m/z 273 (M^+). Found: C, 83.25; H, 5.47; N, 5.09%. Calcd for $\text{C}_{19}\text{H}_{15}\text{NO}$: C, 83.49; H, 5.53; N, 5.13%.

2j: Mp 153°C (from AcOEt); IR (KBr) 1615 and 1640 cm^{-1} ; ^1H NMR (CDCl_3) δ =2.40 (s, 3H, CH_3), 5.30 (s, 2H, CH_2), and 7.11–8.50 (m, 10H, arom); MS (70 eV) m/z 273 (M^+). Found: C, 83.64; H, 5.47; N, 5.05%. Calcd for $\text{C}_{19}\text{H}_{15}\text{NO}$: C, 83.49; H, 5.53; N, 5.13%.

2k: Mp 232°C (from AcOEt); IR (KBr) 1620 and 1649 cm^{-1} ; ^1H NMR (CDCl_3) δ =5.26 (s, 2H, CH_2) and 7.18–8.42 (m, 10H, arom); MS (70 eV) m/z 293 (M^+). Found: C, 73.53; H, 4.06; N, 4.88%. Calcd for $\text{C}_{18}\text{H}_{13}\text{NOCl}$: C, 73.60; H, 4.12; N, 4.77%.

2l: Mp 125°C (from AcOEt); IR (KBr) 1610, 1635, and 3380 cm^{-1} ; ^1H NMR (CDCl_3) δ =3.64–4.14 (m, 5H, CH_2 ×2 and OH), 4.96 (s, 2H, CH_2), and 7.09–8.25 (m, 6H, arom); MS (70 eV) m/z 227 (M^+). Found: C, 73.73; H, 5.77; N, 5.98%. Calcd for $\text{C}_{18}\text{H}_{13}\text{NO}_2$: C, 73.99; H, 5.77; N, 6.16%.

2m: Mp 86°C (from AcOEt); IR (KBr) 1640 and 3375 cm^{-1} ; ^1H NMR (CDCl_3) δ =1.89 (quint, 2H, J =7 Hz, CH_2), 3.55 (q, 2H, J =7 Hz, CH_2), 3.78 (t, 2H, J =7 Hz, CH_2), 4.01 (t, 1H, J =7 Hz, OH), 4.90 (s, 2H, CH_2), and 7.13–8.27 (m, 6H, arom); MS (70 eV) m/z 241 (M^+). Found: C, 74.50; H, 6.31; N, 5.73%. Calcd for $\text{C}_{18}\text{H}_{13}\text{NO}_2$: C, 74.67; H, 6.27; N, 5.80%.

2n: Mp 102°C (from AcOEt); IR (KBr) 1610, 1635, and 3300 cm^{-1} ; ^1H NMR (CDCl_3) δ =1.22 (d, 3H, J =7 Hz, CH_3), 3.51 (d, 2H, J =7 Hz, CH_2), 3.91 (bs, 1H, OH), 4.14 (sext, 1H, J =7 Hz, CH), 4.90 (s, 2H, CH_2), and 6.96–8.12 (m, 6H, arom); MS (70 eV) m/z 241 (M^+). Found: C, 74.27; H, 6.34; N, 5.67%. Calcd for $\text{C}_{18}\text{H}_{13}\text{NO}_2$: C, 74.67; H, 6.27; N, 5.80%.

2o: Mp 103°C (from AcOEt); IR (KBr) 1615, 1640, and 3390 cm^{-1} ; ^1H NMR (CDCl_3) δ =0.95–1.97 (m, 6H, CH_2), 2.24 (s, 1H, OH), 3.53–3.83 (m, 4H, CH_2), 4.95 (s, 2H, CH_2), and 7.23–8.42 (m, 6H, arom); MS (70 eV) m/z 269 (M^+). Found: C, 75.48; H, 7.05; N, 4.92%. Calcd for $\text{C}_{17}\text{H}_{13}\text{NO}_2$: C, 75.81; H, 7.11; N, 5.20%.

2p: Mp 64°C (from AcOEt); IR (KBr) 1610 and 1640 cm^{-1} ; ^1H NMR (CDCl_3) δ =2.20 (quint, 2H, J =7 Hz, CH_2), 3.62 (t, 2H, J =7 Hz, CH_2), 3.75 (t, 2H, J =7 Hz, CH_2), 4.94 (s, 2H, CH_2), and 7.16–8.38 (m, 6H, arom); MS (20 eV) m/z 259 (M^+). Found: C, 69.10; H, 5.47; N, 5.53%. Calcd for $\text{C}_{18}\text{H}_{15}\text{NOCl}$: C, 69.37; H, 5.43; N, 5.39%.

2q: Mp 149°C (from AcOEt); IR (KBr) 1605, 1630, 1720, and 3000 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ =2.76 (t, 2H, J =7 Hz, CH_2), 3.87 (t, 2H, J =7 Hz, CH_2), 5.17 (s, 2H, CH_2), and 7.47–8.52 (m, 7H, arom and COOH); MS (70 eV) m/z 182

(M^+ – $\text{CH}_2\text{CH}_2\text{COOH}$). Found: C, 70.00; H, 5.12; N, 5.43%.

Calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_2$: C, 70.58; H, 5.13; N, 5.49%.

3l: Mp 132°C (from AcOEt); IR (KBr) 1620 and 1640 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$) δ =3.48–4.35 (m, 4H, CH_2), 6.14 (s, 1H, CH), and 7.60–8.35 (m, 6H, arom); MS (70 eV) m/z 225 (M^+). Found: C, 74.59; H, 4.85; N, 6.15%. Calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_2$: C, 74.65; H, 4.92; N, 6.22%.

3m: Mp 126°C (from AcOEt); IR (KBr) 1660 cm^{-1} ; ^1H NMR (CDCl_3) δ =1.52–2.41 (m, 2H, CH_2), 2.90–3.26 (m, 1H, CH), 3.93–4.42 (m, 2H, CH_2), 4.97–5.26 (m, 1H, CH), 6.04 (s, 1H, CH), and 7.44–8.52 (m, 6H, arom); MS (70 eV) m/z 239 (M^+). Found: C, 75.64; H, 5.52; N, 5.94%. Calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_2$: C, 75.30; H, 5.48; N, 5.85%.

3n: Mp 111°C (from AcOEt); IR (KBr) 1670 cm^{-1} ; ^1H NMR (CDCl_3) δ =1.43 (d, 3H, J =7 Hz, CH_3), 3.37 (d, 2H, J =7 Hz, CH_2), 3.01–3.25 (m, 0.09H, CH), 4.18–4.75 (m, 0.91H, CH), 6.05 (s, 0.82H, CH), 6.15 (s, 0.18H, CH), and 7.43–8.30 (m, 6H, arom); MS (70 eV) m/z 239 (M^+). Found: C, 75.47; H, 5.48; N, 5.86%. Calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_2$: C, 75.30; H, 5.48; N, 5.85%.

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